TITLE PAGE:

Added value of contrast-enhanced T1-weighted and diffusion-weighted sequences for characterisation of incidental findings on whole body magnetic resonance imaging (WBMRI) in plasma cell disorders.

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MicroAbstract:

Incidental findings on WBMRI in myeloma may necessitate additional investigations. Incidence, characterisation and significance of incidental findings at WBMRI in 100 patients with plasma cell disorders were calculated. 348 findings were detected in 97/100 patients; 38/348 findings were indeterminate. No additional cancers were detected. Incidental findings are common but the majority can be characterized at WBMRI and are not significant.

Abstract:

Introduction/Background:

Whole body magnetic resonance imaging (WBMRI) is currently recommended by guidelines for the assessment of myeloma. This will inevitably result in incidental findings. We aimed to assess the frequency of extraskeletal incidental findings and the added value of contrast-enhanced T1-weighted (CE T1-W) and diffusion-weighted (DWI) sequences for their characterisation in a single WBMRI examination.

Materials and Methods:

1.5T WBMRI was performed in 100 patients (53 female; median age of 65 years) with plasma cell disorders from January 2014 to July 2017. T2-weighted (T2-W) sequences were reviewed initially for incidental findings, followed by sequential review of T1-W, CE T1-W and DWI sequences for lesion characterisation. Descriptive statistics were undertaken.

Results:

348 incidental findings were detected in 97/100 (97% patients); only 38/348 findings (10.9%) were indeterminate. T1-W sequences increased diagnostic

confidence in the characterisation of 12/38 (31.6%); CE T1-W sequences in the characterisation of 16 of 32 (50%); while DWI increased diagnostic confidence in 21 of 38 (55.3%) compared to the T2-W sequence alone.

Conclusion:

Incidental findings are common but the majority are of no clinical consequence. No additional cancers were noted in our series. DWI and CE T1-W sequences increased diagnostic confidence in 50% of indeterminate findings; and may reduce the need for further investigation.

Keywords:

Multiple myeloma; Magnetic Resonance Imaging; Diffusion Magnetic Resonance Imaging; Whole Body Imaging.

Introduction:

The revised International Myeloma Working Group (IMWG) Guidelines now state that the presence > 1 focal MRI bone lesion > 5 mm is diagnostic of myeloma [1]. IMWG also specifically advocate WBMRI in the initial assessment of smouldering myeloma as patients are at increased risk of progression to myeloma. With its excellent tissue contrast and high spatial resolution, WBMRI provides a comprehensive approach to skeletal and extra-skeletal assessment. WBMRI will define disease burden through the number and location of skeletal lesions, the pattern of disease, and the presence of extra-osseous sites as well as clinically significant complications such as fractures and cord/cauda equina compression.

Thus clinical practice guidelines are changing. Whole body MRI (WBMRI) is now recommended in the United Kingdom (UK) by the National Institute for Health and Care Excellence (NICE) as the first-line imaging test for suspected and newly diagnosed myeloma [2]. The 2017 British Society of Haematology guidelines also recommend WBMRI as the first-line imaging test in asymptomatic patients with 10-60% plasma cells on trephine biopsy or bone marrow aspirate or an M protein > 30g/L [3].

Incidental findings are inevitable with whole body studies and may require further investigations, adding to patient anxiety. Up to 58% of incidental findings may be indeterminate in nature [4]. We hypothesised that a comprehensive WBMRI protocol including T2-weighted (T2-W), T1-weighted (T1-W), contrast-enhanced T1-weighted (CE T1-W) and diffusion-weighted (DWI) sequences will improve the characterisation of incidental findings and potentially reduce the

need for further investigations. Thus we aimed to determine 1) the frequency of incidental findings in patients undergoing WBMRI for plasma cell disorders in our institution; 2) their clinical significance; and 3) the added value of T1-W, CE T1W and DWI sequences in the characterisation of indeterminate findings.

Materials and methods:

Patients

Institutional review board approval was obtained and informed consent waived for this retrospective audit of practice. 100 patients with suspected or proven plasma cell disorders underwent WBMRI between January 2014 and July 2017. There were 53 female, 47 male patients, median age of 65 years (range 38-90 years) with the following confirmed diagnoses: myeloma = 63, smouldering myeloma = 11, monoclonal gammopathy of unknown significance (MGUS) = 12, plasmacytoma = 6 and other diagnoses = 8 (suspected myeloma = 3, amyloidosis = 3, lymphoma = 1, demyelinating neuropathy = 1).

Imaging and image analysis

WBMRI consisting of T2-W, T1-W, DWI (b-value=50 and 900s/mm^2) and CE T1-W sequences from the skull vertex to knees was performed at 1.5T (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) (**Table 1**). WBMRI study duration was approximately 45 minutes. Intravenous contrast administration (20 mLs Dotarem) was only possible in 82/100 (82%) patients due to renal impairment.

T2-W sequences were reviewed initially for incidental findings, followed by a dedicated review of T1-W, CE T1-W and DWI sequences including apparent

diffusion co-efficient (ADC) maps by a staff radiologist with 7 years of MRI experience. Findings, their site, and likely diagnoses were noted. These findings were also categorised as either I -common in asymptomatic subjects/not clinically significant, IIA -benign and potentially clinically significant, IIB -indeterminate and potentially malignant, or III -requiring urgent clinical input, based on review of T2-W sequences.

For indeterminate findings that could not be characterised initially on the T2-W sequence, the likelihood of malignancy was recorded for each additional sequence (T1-W, CE-T1W and DWI) as follows: I = benign, II = probably benign, III = indeterminate, IV = probably malignant, V = malignant.

The diagnostic confidence for likely diagnosis was also scored for T1-W, CE T1-W and DWI sequences independent of each other in order to ascertain the added value of each additional sequence for lesion characterisation compared to the initial T2-W sequence.

Reference standard

Electronic patient records were reviewed in order to confirm whether the incidental findings detected at WBMRI resulted in further investigations, including further imaging tests and biopsy and the final diagnosis. Where no further information was available, clinical consensus as to clinical significance and whether further management would have been undertaken was agreed by 2 haematologists. Clinical significance was graded as follows: unknown, low

significance, moderate significance (meriting further routine investigation) and high significance (meriting urgent investigation).

Statistical analysis:

Descriptive statistics were undertaken using SPSS (Version 24, IBM, Armonk, New York, USA).

Results:

348 incidental findings were detected on the T2-W sequences in 97/100 (97%) patients, (median = 3 findings per patient, range = 1-9 findings). The most common findings are summarised in **Table 2.**

197/348 (56.6%) findings were classified as category I (benign/not clinically significant), 113/348 (32.5%) findings were classified as category IIA (benign and potentially clinically significant) and 38/348 (10.9%) findings were classified as category IIB. (Indeterminate and potentially malignant). There were no category III (clinically urgent) findings.

The category IIB (indeterminate) findings are summarised in **Table 3** and were located at the following sites: liver (7), spleen (2), adrenal (5), prostate (5), lymph nodes (5) and others (14). Thirty-four patients had one indeterminate finding; 2 patients had 2 indeterminate findings; 2 patients had 3 and 4 indeterminate findings respectively.

Each additional sequence (T1-W, CE T1-W or DWI) resulted in increased diagnostic confidence for lesion characterisation when compared with the initial T2-weighted imaging. T1-weighted Dixon sequences increased diagnostic confidence in the characterisation of 12/38 (31.6%) findings due to its ability to demonstrate microscopic fat and haemorrhage; 5 indeterminate adrenal lesions were confirmed as adrenal adenomas with the T1-W Dixon sequences. CE T1-W sequences, only possible in 82/100 (82%) patients due to renal impairment in the remaining patients, increased diagnostic confidence in characterisation of 16 of 32 (50%) findings compared to T2-W imaging alone and was particularly helpful for hepatic and renal lesions. DWI sequences increased diagnostic confidence in characterisation of 21 of 38 (55.3%) findings compared to T2-W imaging alone. T1-weighted Dixon, DWI and CE T1-W sequences did not improve characterisation of 2 subcentimetre pulmonary nodules.

In 16/38 (42.1%) patients further investigation of indeterminate findings was recommended (further imaging = 5, histology = 11). 8/16 (50%) patients were investigated further. For the remaining 8 findings, one patient died before further investigation could be undertaken. The cause of death was progressive myeloma and the hepatosplenic lesions likely represented extramedullary disease sites. Of the 7 findings not investigated initially, 5/7 findings scored as low clinical significance. 2/7 findings were scored as moderate by clinical consensus, for whom further investigations were recommended; transvaginal ultrasound in Patient 5, found to have incidental endometrial thickening, and serum PSA +/- histology in Patient 7 with possible incidental prostatic lesion (**Table 4**).

No additional new malignancies were detected in this cohort. There were 3 cases of known concurrent malignancy (prostate cancer (2) and parotid Warthin's tumour (1)). There were also 2 cases of extramedullary plasmacytoma within lymph nodes. Following exclusion of the 3 cases of known malignancy, 19/35 (54.3%) indeterminate findings could be fully characterised via T1-Dixon, DWI and/or CE T1-W sequences such that no further investigations were required.

Discussion:

Incidental findings are relatively common in patients with plasma cell disorders undergoing WBMRI, present in 97% of patients in our cohort. The majority could be characterised fully with a comprehensive protocol such that no further investigations were required. Over half of the detected incidental findings were classified as not clinically significant or common in asymptomatic subjects. No new malignancies were detected in our cohort although there were pre-existing malignancies and extra-osseous sites of disease.

T1-W Dixon sequences were helpful in the characterisation of lesions containing microscopic fat e.g. adrenal adenoma, macroscopic fat e.g. lipoma and in the detection of haemorrhage e.g. haemorrhagic material within the uterine cavity and haemorrhagic renal cysts. CE T1-W sequences were particularly helpful in characterisation of hepatic and renal lesions. Diffusion-weighted sequences assisted in the characterisation of prostatic lesions, hepatic lesions and lymph nodes.

Our study reports a higher percentage of incidental findings than previously published WBMRI studies of various populations, where incidental findings have been found in up to 80% of patients [5]. In the general population-based Study of Health in Pomerania (SHIP), incidental findings were detected in 36.2% of participants (n= 2500), 5.9% of which were malignant [4]. In the SHIP study, incidental findings were categorised as either I -normal/common in asymptomatic subjects, II -requiring further medical evaluation or III -requiring immediate referral. In another study incidental findings were detected in 42% of neurofibromatosis patients (n=247) [6] whilst, amongst a cohort of lymphoma patients (n=119), 79.8% had one or more incidental finding although only 6% were classified as clinically significant [5].

There is only one other study to date evaluating incidental findings in WBMRI in myeloma where incidental findings were detected in 38% of patients [7]. In this retrospective study the authors reviewed WBMRI (comprising axial DWI sequences with corresponding ADC maps and T1-W and T2-W sagittal whole spine sequences) in 110 patients. 70 incidental findings were documented, of which 14/70 (20%) were equivocal or indeterminate. Clinical correlation/review of previous imaging was recommended as the initial action in 57% (8/14 patients) with indeterminate incidental findings and only 3% required further characterisation as the initial action.

The comparatively higher incidental finding detection rate in our cohort compared with this study partly reflects the differences in imaging protocol. The WBMRI protocol utilised in the study by Wale et al only included axial DWI

sequences compared to our more comprehensive protocol of T2-W, T1-W, CE T1-W and DWI sequences. Greater standardisation of WBMRI protocols could reduce such variances. The greater proportion of incidental findings requiring further investigation in our cohort may also be partially attributed to variations in individual radiologist threshold for reporting some incidental findings and also intrinsic differences in the incidental findings encountered. For example, no prostatic lesions were reported in the study by Wale et al.

There are no studies to date that have specifically addressed the value of individual sequences in characterising incidental findings. The value of diffusion-weighted sequences in the baseline assessment of focal and diffuse marrow infiltration is clear (8) and there is growing evidence for its use in myeloma response assessment (9). Contrast-enhanced sequences are not utilised in all WBMRI protocols, particularly given the prevalence of renal impairment in this population, however studies have shown that they improve sensitivity for detection of bone lesions (10), hence the inclusion of post-contrast imaging in our WBMRI protocol. This study demonstrates that both DWI and CE T1-W imaging increased diagnostic confidence in characterisation of incidental findings.

Nevertheless, there are limitations to this study. Incidental findings were recorded regardless of clinical importance, thus our detection rate is likely to exceed that of a typical clinical report. Secondly, due to its retrospective nature, it was not possible to determine if further investigation of indeterminate findings had been actioned in all patients, even after electronic patient record

review. However of the 7 cases identified, only 2 were considered of moderate clinical significance by clinical consensus. Additionally, only one reader performed the imaging analysis, thus intra and inter-observer variation could not be assessed. It is also theoretically possible that additional incidental findings could be demonstrated on supplementary sequences such as CE T1-W sequences e.g. hypervascular hepatosplenic lesions, however this potential issue was not encountered in our study cohort. Finally, the grading score used to assess malignancy likelihood of indeterminate findings has not been validated for use in previous studies. This study could be further improved by incorporating a second reader and utilizing a prospective approach.

Conclusion:

Incidental findings are relatively common in patients with plasma cell disorders undergoing WBMRI. The majority of findings are benign in nature and can be characterised fully with a comprehensive protocol, necessitating few additional investigations. Our findings should provide reassurance to clinicians requesting WBMRI.

Clinical Practice Points:

There has only been one previous study assessing frequency and significance of incidental findings at WBMRI in myeloma where incidental findings were detected in 38% of patients. In our study, the detection rate is significantly higher (97%). This difference may be explained by differences in imaging protocol and by variations in individual radiologist threshold for reporting some incidental findings.

The results of this study demonstrate that, whilst incidental findings are common at whole body MRI (WBMRI), the vast majority are not clinically significant. The inclusion of contrast-enhanced and diffusion-weighted sequences in WBMRI protocols substantially improves reader confidence in characterization of incidental findings, reducing the need for further additional investigations (potentially resulting in patient anxiety and additional healthcare costs).

Our results should provide reassurance to clinicians requesting WBMRI with regards possible incidental findings, and provide further evidence to support inclusion of contrast-enhanced and diffusion-weighted sequences in WBMRI protocols, additional to their value in detection of bone disease in myeloma.

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